Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

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Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 1 of 19)

This table provides information on the known or predicted interactions between PIs and non-ARV drugs. When information is available, interactions for boosted ATV (with either RTV or COBI) and unboosted ATV are listed separately. The term "All PIs" refers to both unboosted ATV and PIs boosted with either RTV or COBI, except for FPV, IDV, NFV, and SQV. For information regarding interactions between PIs and other ARV drugs, including dosing recommendations, refer to Tables 21c, 22a, and 22b.

Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. In cases where an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgement to select the most appropriate alternative medication to use.

Note: FPV, IDV, NFV, and SQV are no longer commonly used in clinical practice and are **not** included in this table. Please refer to the FDA product labels for FPV, IDV, NFV, and SQV for information regarding drug interactions between these PIs and concomitant medications.

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV, ATV/c, ATV/r	**When Given Simultaneously:** • ↓ ATV expected	Administer ATV at least 2 hours before or 1–2 hours after antacids or buffered medications.
	TPV/r	TPV AUC ↓ 27%	Administer TPV at least 2 hours before or 1 hour after antacids.
H2 Receptor Antagonists	ATV (unboosted)	**When Given Simultaneously with Famotidine:** • ATV AUC ↓ 41% **When Given 2 Hours Before and ≥10 Hours After H2RA:** • ↔ ATV	A single dose of H2RA should not exceed a dose equivalent to famotidine 20 mg, and the total daily dose should not exceed a dose equivalent to famotidine 20 mg twice daily in PI-naive patients. Give ATV at least 2 hours before and at least 10 hours after the H2RA. **Do not coadminister** unboosted ATV plus H2RA in PI-experienced patients.
	ATV/c, ATV/r	↓ ATV expected	H2RA dose should not exceed a dose equivalent to famotidine 40 mg twice daily in ART-naive patients or famotidine 20 mg twice daily in ART-experienced patients. Give ATV 300 mg (plus COBI 150 mg **or** RTV 100 mg) simultaneously with and/or ≥10 hours after the dose of H2RA. If using TDF and H2RA in ART-experienced patients, use ATV 400 mg (plus COBI 150 mg **or** RTV 100 mg).
	DRV/c, DRV/r, LPV/r, TPV/r	**With Ranitidine:** • ↔ DRV/r ↔ PI expected	No dose adjustment needed.
Proton Pump Inhibitors	ATV (unboosted)	**With Omeprazole 40 mg:** • ATV AUC ↓ 94%	**Do not coadminister**.
	ATV/c, ATV/r	**With Omeprazole 40 mg:** • ATV AUC ↓ 76% **When Omeprazole 20 mg is Given 12 Hours before ATV/c or ATV/r:** • ATV AUC ↓ 42%	PPI dose should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naive patients. PPIs should be administered at least 12 hours before ATV/c or ATV/r. **Do not coadminister in PI-experienced patients.**

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers, continued			
Proton Pump Inhibitors	DRV/c, LPV/r	↔ PI expected	No dose adjustment needed.
	DRV/r	↔ DRV/r Omeprazole AUC ↓ 42%	Consider alternative ARV or acid reducer. If coadministered, monitor for omeprazole efficacy. If patient does not experience symptomatic relief, increase dose to no more than omeprazole 40 mg daily.
	TPV/r	↔ TPV/r Omeprazole AUC ↓ 70%	**Do not coadminister**.
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin	All PIs	↑ alfuzosin expected	**Contraindicated.**
Doxazosin	All PIs	↑ doxazosin possible	Initiate doxazosin at lowest dose and titrate while monitoring for clinical response/adverse events. Dose reduction may be necessary.
Tamsulosin	All PIs	↑ tamsulosin expected	**Do not coadminister, unless benefits outweigh risks.** If coadministered, monitor for tamsulosin toxicities.
Terazosin	All PIs	↔ or ↑ terazosin possible	Initiate terazosin at lowest dose and titrate while monitoring for clinical response/adverse events. Dose reduction may be necessary.
Silodosin	All PIs	↑ silodosin expected	**Contraindicated.**
Antibacterials			
Antimycobacterials			
Bedaquiline	All PIs	**With LPV/r:** • Bedaquiline AUC ↑ 1.9-fold **With other PI/r, ATV/c, or DRV/c:** • ↑ bedaquiline possible	**Do not coadminister, unless benefits outweigh risks.** Monitor liver function and ECG for QTc prolongation.
Rifabutin	ATV (unboosted)	↑ rifabutin AUC expected	Recommended dose is rifabutin 150 mg once daily. Monitor for antimycobacterial activity and consider therapeutic drug monitoring. PK data in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in patients with HIV than in healthy study participants.
	ATV/r	**Compared with Rifabutin (300 mg Once Daily) Alone, Rifabutin (150 mg Once Daily) plus ATV/r:** • Rifabutin AUC ↑ 110% and metabolite AUC ↑ 2,101%	
	DRV/r	**Compared with Rifabutin (300 mg Once Daily) Alone, Rifabutin (150 mg Every Other Day) plus DRV/r:** • ↔ rifabutin AUC and metabolite AUC ↑ 881%	
	LPV/r	**Compared with Rifabutin (300 mg Daily) Alone, Rifabutin (150 mg Once Daily) plus LPV/r:** • Rifabutin AUC ↑ 203% and metabolite AUC ↑ 375%	
	TPV/r	Rifabutin AUC ↑ 190% and metabolite AUC ↑ 1,971%	
	PI/c	↑ rifabutin expected ↓ COBI expected	**Do not coadminister.**

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 3 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antibacterials, continued			
Antimycobacterials, continued			
Rifampin	All PIs	↓ PI concentration by >75%	**Contraindicated.** Increasing the dose of RTV does not overcome this interaction and may increase hepatotoxicity. Increasing the COBI dose is not recommended. Consider rifabutin if a rifamycin is indicated.
Rifapentine	All PIs	↓ PI expected	**Do not coadminister**.
Macrolides			
Azithromycin	ATV (unboosted), ATV/c, ATV/r	↑ azithromycin possible	No dose adjustment needed.
	DRV/c, DRV/r, TPV/r	↔ azithromycin expected	No dose adjustment needed.
Clarithromycin	ATV (unboosted)	Clarithromycin AUC ↑ 94%	Reduce clarithromycin dose by 50% or consider alternative ARV or azithromycin. Monitor for clarithromycin-related adverse events, including QTc prolongation.
	PI/c, PI/r	DRV/r ↑ clarithromycin AUC 57% LPV/r ↑ clarithromycin expected RTV 500 mg twice daily ↑ clarithromycin 77% TPV/r ↑ clarithromycin 19% Clarithromycin ↑ TPV 66%	Consider alternative ARV or azithromycin. Monitor for clarithromycin-related adverse events, including QTc prolongation. If use of clarithromycin is necessary in a patient with impaired renal function, reduce clarithromycin dose by 50% in patients with CrCl 30 to 60 mL/min. In patients with CrCl <30 mL/min, reduce clarithromycin dose by 75%.
Erythromycin	All PIs	↑ erythromycin expected ↑ PIs expected	Consider alternative ARV or use azithromycin.
Anticoagulants			
Apixaban	ATV (unboosted)	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
	PI/c, PI/r	↑ apixaban expected	**Do not coadminister** in patients who require apixaban 2.5 mg twice daily. **In Patients Requiring Apixaban 5 mg or 10 mg Twice Daily:** • Reduce apixaban dose by 50%.
Betrixaban	ATV (unboosted)	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
	ATV/c, ATV/r, LPV/r	↑ betrixaban expected	Administer an initial single dose of betrixaban 80 mg followed by betrixaban 40 mg once daily.
	DRV/c, DRV/r, TPV/r	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
Dabigatran	ATV (unboosted)	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
	ATV/c, ATV/r, LPV/r	↑ dabigatran expected **With COBI 150 mg Alone:** • Dabigatran AUC ↑ 110% to 127%	Dabigatran dosing recommendation depends on indication and renal function. Refer to dabigatran prescribing information for dosing instructions when using dabigatran concomitantly with P-glycoprotein inhibitors.
	DRV/c, DRV/r, TPV/r	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 4 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants, continued			
Edoxaban	ATV (unboosted)	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
	ATV/c, ATV/r, LPV/r	↑ edoxaban expected	**Stroke Prevention in Nonvalvular Atrial Fibrillation Indication:** • No dose adjustment needed. **Deep Venous Thrombosis and Pulmonary Embolism Indication:** • Administer edoxaban 30 mg once daily.
	DRV/c, DRV/r, TPV/r	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
Rivaroxaban	ATV (unboosted)	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
	PI/c, PI/r	↑ rivaroxaban expected	**Do not coadminister**.
Warfarin	PI/c	No data	Monitor INR closely when stopping or starting PI/c or PI/r and adjust warfarin dose accordingly. If switching between RTV and COBI, the effect of COBI on warfarin is not expected to be equivalent to RTV's effect on warfarin.
	PI/r	↓ warfarin possible	
Anticonvulsants			
Carbamazepine	ATV (unboosted)	May ↓ PI concentrations substantially	**Do not coadminister**.
	ATV/r, LPV/r, TPV/r	↑ carbamazepine possible TPV/r ↑ carbamazepine AUC 26% May ↓ PI concentrations substantially	Consider alternative ARV or anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
	DRV/r	Carbamazepine AUC ↑ 45% ↔ DRV	Monitor anticonvulsant concentration and adjust dose accordingly.
	PI/c	↑ carbamazepine possible ↓ cobicistat expected ↓ PI expected	**Contraindicated.**
Eslicarbazepine	All PIs	↓ PI possible	Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor for virologic response. Consider monitoring anticonvulsant and PI concentrations.
Ethosuximide	All PIs	↑ ethosuximide possible	Monitor for ethosuximide-related adverse events.
Lamotrigine	ATV (unboosted)	↔ lamotrigine	No dose adjustment needed.
	ATV/r	Lamotrigine AUC ↓ 32%	A dose increase of lamotrigine may be needed; monitor lamotrigine concentration or consider alternative ARV or anticonvulsant.
	LPV/r	Lamotrigine AUC ↓ 50% ↔ LPV	
	DRV/r, TPV/r	↓ lamotrigine possible	
	PI/c	No data	Monitor anticonvulsant concentration and adjust dose accordingly.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 5 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants, continued			
Oxcarbazepine	All PIs	↓ PI possible	Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor for virologic response. Consider monitoring anticonvulsant and PI concentrations.
Phenobarbital	ATV (unboosted)	↓ ATV expected	**Do not coadminister**.
	ATV/r, DRV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assessing virologic response.
	LPV/r	↓ phenytoin possible ↓ LPV/r possible	**Do not coadminister with LPV/r once daily.** Consider alternative anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assessing virologic response.
	PI/c	↓ cobicistat expected ↓ PI expected	**Contraindicated.**
Phenytoin	ATV (unboosted)	↓ ATV expected	**Do not coadminister**.
	ATV/r, DRV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assessing virologic response.
	LPV/r	Phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	**Do not coadminister with LPV/r once daily.** Consider alternative anticonvulsant or monitor concentrations of both drugs and assess virologic response.
	PI/c	↓ cobicistat expected ↓ PI expected	**Contraindicated.**
Valproic Acid	All PIs	↓ or ↔ VPA possible LPV AUC ↑ 38% No data for other PIs	Monitor VPA concentrations and monitor for PI tolerability.
Antidepressants, Anxiolytics, and Antipsychotics Also see Sedative/Hypnotics section below			
Bupropion	ATV/r, DRV/r	↓ bupropion possible	Titrate bupropion dose based on clinical response.
	TPV/r	Bupropion AUC ↓ 46%	
	LPV/r	Bupropion AUC ↓ 57%	
	PI/c	↔ bupropion expected	No dose adjustment needed.
Buspirone	All PIs	↑ buspirone expected	Administer lowest dose of buspirone with caution and titrate buspirone dose based on clinical response.
Nefazodone	All PIs	↑ nefazodone expected ↑ PI possible	Monitor for nefazodone-related adverse events and PI tolerability.
Trazodone	All PIs	RTV 200 mg twice daily (for 2 days) ↑ trazodone AUC 240%	Administer lowest dose of trazodone and monitor for CNS and CV adverse events.

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants, Anxiolytics, and Antipsychotics, continued Also see Sedative/Hypnotics section below			
Tricyclic Antidepressants Amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine	All PIs	↑ TCA expected	Administer lowest possible TCA dose and titrate based on clinical assessment and/or drug concentrations.
Selective Serotonin Reuptake Inhibitors (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)	DRV/r	Paroxetine AUC ↓ 39% Sertraline AUC ↓ 49%	Titrate SSRI dose based on clinical response.
	All PIs except DRV/r	No data	Titrate SSRI dose using the lowest available initial or maintenance dose.
Antipsychotics			
Aripiprazole	PI/c, PI/r	↑ aripiprazole expected	Administer 25% of the usual aripiprazole dose. Titrate dose based on clinical monitoring for efficacy/adverse events. Refer to aripiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
	ATV (unboosted)	↑ aripiprazole expected	Administer 50% of the usual aripiprazole dose. Titrate dose based on clinical monitoring for efficacy/adverse events. Refer to aripiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
Brexpiprazole	PI/c, PI/r	↑ brexpiprazole expected	Administer 25% of the usual brexpiprazole dose. Titrate dose based on clinical monitoring for efficacy/adverse events. Refer to brexpiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
	ATV (unboosted)	↑ brexpiprazole expected	Administer 50% of the usual brexpiprazole dose. Titrate dose based on clinical monitoring for efficacy/adverse events. Refer to brexpiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
Cariprazine	All PIs	↑ cariprazine expected	**Starting Cariprazine in a Patient Who Is Already Receiving a PI:** • Administer cariprazine 1.5 mg on Day 1 and Day 3, with no dose given on Day 2. From Day 4 onward, administer cariprazine 1.5 mg daily. Dose can be increased to a maximum dose of cariprazine 3 mg daily. If the PI is withdrawn, cariprazine dose may need to be increased. **Starting a PI in a Patient Who Is Already Receiving Cariprazine:** • For patients receiving cariprazine 3 mg or cariprazine 6 mg daily, reduce dose by half. For patients taking cariprazine 4.5 mg daily, the dose should be reduced to cariprazine 1.5 mg or cariprazine 3 mg daily. For patients taking cariprazine 1.5 mg daily, change to cariprazine 1.5 mg every other day. If PI is withdrawn, cariprazine dose may need to be increased.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 7 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants, Anxiolytics, and Antipsychotics, continued Also see Sedative/Hypnotics section below			
Antipsychotics, continued			
Iloperidone	All PIs	↑ iloperidone expected	Decrease iloperidone dose by 50%.
Lurasidone	ATV (unboosted)	↑ lurasidone expected	Consider alternative ARV or antipsychotic. If coadministration is necessary, reduce lurasidone dose by 50%.
	PI/c, PI/r	↑ lurasidone expected	**Contraindicated.**
Other Antipsychotics CYP3A4 and/or CYP2D6 substrates (e.g., clozapine, perphenazine, risperidone, thioridazine)	PI/c, PI/r	↑ antipsychotic possible	Titrate antipsychotic dose using the lowest initial dose or adjust maintenance dose accordingly. Monitor for adverse events, including QTc prolongation.
Pimavanserin	ATV (unboosted)	No data	No data available for dose recommendation. Consider alternative ARV or antipsychotic.
	LPV/r	↑ pimavanserin expected	**Do not coadminister**, due to risk for QTc prolongation.
	All other PIs	↑ pimavanserin expected	Reduce pimavanserin dose to 10 mg once daily.
Pimozide	All PIs	↑ pimozide expected	**Contraindicated.**
Quetiapine	All PIs	↑ quetiapine expected	**Starting Quetiapine in a Patient Receiving a PI:** • Initiate quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine effectiveness and adverse events. **Starting a PI in a Patient Receiving a Stable Dose of Quetiapine:** • Reduce quetiapine dose to 1/6 of the current dose. Closely monitor for quetiapine effectiveness and adverse events.
Ziprasidone	LPV/r	↑ ziprasidone expected	**Do not coadminister,** due to risk for QTc prolongation.
	All PIs except LPV/r	↑ ziprasidone expected	Monitor for ziprasidone-related adverse events.
Antifungals			
Fluconazole	TPV/r	TPV AUC ↑ 50%	Fluconazole doses >200 mg daily **are not recommended**. If high-dose fluconazole is indicated, consider alternative ARV.
	All PIs except TPV/r	↔ PI expected ↔ fluconazole expected	No dose adjustment needed.
Isavuconazole	LPV/r	Isavuconazole AUC ↑ 96% LPV AUC ↓ 27% RTV AUC ↓ 31%	If coadministered, monitor isavuconazole concentrations and adverse events. Monitor for virologic response.
	All PIs except LPV/r	↑ isavuconazole possible ↑ or ↓ PI possible	If coadministered, monitor isavuconazole concentrations and monitor for isavuconazole-related adverse events. Monitor for PI tolerability and virologic response.
Itraconazole	All PIs	↑ itraconazole possible ↑ PI possible	Itraconazole doses >200 mg/day **are not recommended** with PI/r, ATV/c, or DRV/c unless dosing is guided by itraconazole concentrations.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 8 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals, continued			
Posaconazole	ATV	ATV AUC ↑ 268% ↑ posaconazole possible	If coadministered, monitor posaconazole concentrations and monitor for posaconazole-related or PI-related adverse events.
	ATV/r	ATV AUC ↑ 146% ↑ posaconazole possible	
	All other PIs	↑ PI possible ↑ posaconazole possible	
Voriconazole	ATV (unboosted)	↑ PI possible ↑ voriconazole possible	If coadministered, monitor voriconazole concentrations and monitor for voriconazole-related or PI-related adverse events.
	PI/c	No data	**Do not coadminister** voriconazole and RTV or COBI unless benefits outweigh risks. If coadministered, monitor voriconazole concentration and adjust dose accordingly.
	PI/r	RTV 100 mg twice daily ↓ voriconazole AUC 39%	
Antimalarials			
Artemether/ Lumefantrine	ATV (unboosted), PI/c	↑ lumefantrine expected No data for artemether	Clinical significance unknown. If coadministered, monitor closely for antimalarial efficacy and lumefantrine toxicity, including QTc prolongation.
	DRV/r	Artemether AUC ↓ 16% DHA[a] AUC ↓ 18% Lumefantrine AUC ↑ 175% ↔ DRV	
	LPV/r	Artemether AUC ↓ 40% DHA AUC ↓ 45% Lumefantrine AUC ↑ 4.8-fold ↔ LPV	
	TPV/r	↑ lumefantrine expected	**Do not coadminister**, due to risk for QTc prolongation.
Atovaquone/Proguanil	ATV/r, LPV/r	**With ATV/r:** • Atovaquone AUC ↓ 46% • Proguanil AUC ↓ 41% **With LPV/r:** • Atovaquone AUC ↓ 74% • Proguanil AUC ↓ 38%	Clinical significance unknown. Consider alternative ARV or malaria prophylaxis.
Mefloquine	All PIs	**With RTV 200 mg Twice Daily:** • RTV AUC ↓ 31% and C_{min} ↓ 43% • ↔ mefloquine **With ATV (unboosted), PI/c, or PI/r:** • No data • ↑ mefloquine possible	Clinical significance unknown. Consider alternative ARV or antimalarial drug. If coadministered, monitor for mefloquine-related adverse events, including psychiatric symptoms and QTc prolongation. Monitor virologic response.

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antiplatelets			
Clopidogrel	All PIs	Clopidogrel active metabolite AUC ↓ 320% with impaired platelet inhibition	**Do not coadminister.**
Prasugrel	All PIs	Prasugrel active metabolite AUC ↓ 210% with adequate platelet inhibition	Insufficient data to make a recommendation.
Ticagrelor	All PIs	↑ ticagrelor expected	**Do not coadminister**.
Vorapaxar	All PIs	↑ vorapaxar expected	**Do not coadminister**.
Antipneumocystis and Antitoxoplasmosis Drug			
Atovaquone	ATV/r	↔ atovaquone	No dose adjustment needed.
Oral suspension	All other PIs	↔ atovaquone expected	No dose adjustment needed.
Beta-Agonists, Long-Acting Inhaled			
Arformoterol, Formoterol	ATV (unboosted), ATV/c, ATV/r	↑ arformoterol possible	No dose adjustment needed.
	DRV/c, DRV/r, LPV/r, TPV/r	↔ arformoterol expected	No dose adjustment needed.
Indacaterol	All PIs	**With RTV 300 mg Twice Daily:** • Indacaterol AUC ↑ 1.7-fold	No dose adjustment needed in patients receiving indacaterol 75 mcg daily.
Olodaterol	All PIs	↑ olodaterol expected	No dose adjustment needed.
Salmeterol	All PIs	↑ salmeterol possible	**Do not coadminister**, due to potential increased risk of salmeterol-associated CV events.
Cardiac Medications			
Amiodarone	TPV/r	↑ amiodarone possible ↑ PI possible	**Contraindicated.**
	All other PIs	↑ amiodarone possible ↑ PI possible	**Do not coadminister** unless benefits outweigh risks. If coadministered, monitor for amiodarone-related adverse events and consider monitoring ECG and amiodarone drug concentration.
Antiarrhythmics (e.g., disopyramide, dofetilide, lidocaine, mexiletine, propafenone)	ATV (unboosted)	↑ antiarrhythmic possible	Consider alternative ARV or antiarrhythmics. If coadministered, monitor for antiarrhythmic toxicities.
	PI/c, PI/r	↑ antiarrhythmic possible	**Do not coadminister**.
Dronedarone	ATV (unboosted)	↑ dronedarone possible	**Do not coadminister**.
	PI/c, PI/r	↑ dronedarone expected	**Contraindicated.**
Flecainide	All PIs except TPV/r	↑ flecainide possible	**Do not coadminister**.
	TPV/r	↑ flecainide expected	**Contraindicated.**
Propafenone	All PIs except TPV/r	↑ propafenone possible	**Do not coadminister**.
	TPV/r	↑ propafenone expected	**Contraindicated.**
Quinidine	All PIs except TPV/r	↑ quinidine possible	**Do not coadminister**.
	TPV/r	↑ quinidine expected	**Contraindicated.**

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 10 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications, continued			
Beta-Blockers (e.g., carvedilol, metoprolol, timolol)	All PIs	↑ beta-blockers possible	May need to decrease beta-blocker dose; adjust dose based on clinical response. Consider using beta-blockers that are not metabolized by CYP450 enzymes (e.g., atenolol, labetalol, nadolol, sotalol).
Bosentan	All PIs	**With LPV/r:** • ↑ bosentan 48-fold (Day 4) and ↑ 5-fold (Day 10) ↓ ATV expected	**Do not coadminister bosentan and unboosted ATV.** **In Patients on a PI (Other than Unboosted ATV) >10 Days:** • Start bosentan at 62.5 mg once daily or every other day. **In Patients on Bosentan who Require a PI (Other than Unboosted ATV):** • Stop bosentan ≥36 hours before PI initiation and restart bosentan 10 days after PI initiation at 62.5 mg once daily or every other day. **When Switching Between COBI and RTV:** • Maintain same bosentan dose.
Calcium Channel Blockers, Except Diltiazem	All PIs	↑ dihydropyridine possible ↑ verapamil possible	Titrate CCB dose and monitor closely. ECG monitoring is recommended when CCB is used with ATV.
Digoxin	PI/c, PI/r	RTV 200 mg twice daily ↑ digoxin AUC 29% and ↑ half-life 43% DRV/r ↑ digoxin AUC 36% COBI ↑ digoxin C_{max} 41% and ↔ AUC	Monitor digoxin concentrations. Digoxin dose may need to be decreased. Titrate initial digoxin dose.
Diltiazem	ATV (unboosted), ATV/c, ATV/r	Unboosted ATV ↑ diltiazem AUC 125% Greater ↑ likely with ATV/c or ATV/r	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/c, DRV/r, LPV/r, TPV/r	↑ diltiazem possible	Titrate diltiazem dose according to clinical response and toxicities.
Eplerenone	PI/c, PI/r	↑ eplerenone expected	**Contraindicated.**
Ranolazine	ATV (unboosted)	↑ ranolazine possible	**Do not coadminister**.
	PI/c, PI/r	↑ ranolazine expected	**Contraindicated.**
Ivabradine	All PIs	↑ ivabradine expected	**Contraindicated.**
Corticosteroids			
Beclomethasone Inhaled or intranasal	DRV/r	↔ 17-BMP (active metabolite) AUC RTV 100 mg twice daily ↑ 17-BMP AUC 2-fold	No dose adjustment needed.
	All PIs except DRV/r	↔ 17-BMP expected	No dose adjustment needed.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 11 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids, continued			
Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal	All PIs	↑ glucocorticoids possible RTV 100 mg twice daily ↑ fluticasone AUC 350-fold	**Do not coadminister** unless potential benefits of inhaled or intranasal corticosteroid outweigh the risks of adverse events associated with corticosteroids. Coadministration can result in adrenal insufficiency and Cushing's syndrome. Consider alternative inhaled/intranasal corticosteroid (e.g., beclomethasone).
Betamethasone, Budesonide Systemic	All PIs	↑ glucocorticoids possible ↓ PI possible	**Do not coadminister** unless potential benefits of systemic corticosteroid outweigh the risks of adverse events associated with systemic corticosteroids. Coadministration can result in adrenal insufficiency and Cushing's syndrome.
Dexamethasone Systemic	All PIs	↑ glucocorticoids possible ↓ PI possible	Consider alternative corticosteroid for long-term use. If coadministration is necessary, monitor virologic response to ART.
Prednisone, Prednisolone Systemic	LPV/r	↑ prednisolone AUC 31%	Coadministration may be considered if the potential benefits outweigh the risks of adverse events associated with systemic corticosteroids. If coadministered, monitor for adrenal insufficiency, Cushing's syndrome, and other corticosteroid-associated toxicities.
	All PIs	↑ prednisolone possible	
Betamethasone, Methylprednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital	All PIs	↑ glucocorticoids expected	**Do not coadminister**. Coadministration can result in adrenal insufficiency and Cushing's syndrome.
Glucose-Lowering Medications			
Canagliflozin	ATV (unboosted), PI/c	↔ canagliflozin	No dose adjustment needed.
	PI/r	↓ canagliflozin expected	If a patient is already tolerating canagliflozin 100 mg daily, increase canagliflozin dose to 200 mg daily. If a patient is already tolerating canagliflozin 200 mg daily and requires additional glycemic control, management strategy is based on renal function. **In Patients with eGFR ≥60 mL/min/1.73 m²:** • Canagliflozin dose may be increased to 300 mg daily. **In Patients with eGFR <60 mL/min/1.73 m²:** • Consider adding another antihyperglycemic agent.
Saxagliptin	All PIs	↑ saxagliptin expected	Limit saxagliptin dose to 2.5 mg once daily.
Dapagliflozin/Saxagliptin	All PIs	↑ saxagliptin expected	**Do not coadminister.** Dapagliflozin is only available as a coformulated drug that contains 5 mg of saxagliptin. When coadministered with EVG/c, the dose of saxagliptin should not exceed 2.5 mg once daily; thus, this combination **is not recommended**.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 12 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	ATV/c, ATV/r	↑ daclatasvir	Decrease daclatasvir dose to 30 mg once daily.
	ATV (unboosted), DRV/c, DRV/r, LPV/r	↔ daclatasvir	No dose adjustment needed.
	TPV/r	No data	No data available for dose recommendation.
Dasabuvir plus Paritaprevir/Ombitasvir/ RTV	ATV (unboosted)	↔ ATV	ATV 300 mg alone, **without COBI or additional RTV**, should be given in the morning with dasabuvir plus paritaprevir/ombitasvir/RTV.
	ATV/c, ATV/r	No data	This HCV regimen contains RTV. If ATV is part of the ARV regimen, prescribe ATV 300 mg daily without COBI or RTV. ATV should be administered in the morning, at the same time as ombitasvir/paritaprevir/RTV plus dasabuvir. Resume RTV or COBI regimen when HCV therapy is completed.
	DRV	DRV C_{min} ↓ 43% to 48%	**Do not coadminister**.
	LPV/r	Paritaprevir AUC ↑ 117%	**Do not coadminister**.
	DRV/c, TPV/r	No data	**Do not coadminister**.
Elbasvir/Grazoprevir	ATV/r	Elbasvir AUC ↑ 4.8-fold Grazoprevir AUC ↑ 10.6-fold Elbasvir ↔ ATV Grazoprevir ↑ ATV AUC 43%	**Contraindicated.** May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition.
	DRV/r	Elbasvir AUC ↑ 66% Grazoprevir AUC ↑ 7.5-fold ↔ DRV	
	LPV/r	Elbasvir AUC ↑ 3.7-fold Grazoprevir AUC ↑ 12.9-fold ↔ LPV	
	ATV (unboosted), ATV/c, DRV/c, TPV/r	↑ grazoprevir expected	

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 13 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
Glecaprevir/Pibrentasvir	ATV (unboosted), ATV/c, ATV/r	**With (ATV 300 mg plus RTV 100 mg) Once Daily:** • Glecaprevir AUC ↑ 6.5-fold • Pibrentasvir AUC ↑ 64%	**Contraindicated.**
	DRV/c, DRV/r	**With (DRV 800 mg plus RTV 100 mg) Once Daily:** • Glecaprevir AUC ↑ 5-fold • ↔ pibrentasvir	**Do not coadminister**.
	LPV/r	Glecaprevir AUC ↑ 4-fold Pibrentasvir ↑ 2.5-fold	**Do not coadminister**.
	TPV/r	↑ glecaprevir and pibrentasvir expected	**Do not coadminister**.
Ledipasvir/Sofosbuvir	ATV/r	ATV AUC ↑ 33% Ledipasvir AUC ↑ 113% ↔ sofosbuvir	No dose adjustment needed. Coadministration of ledipasvir/sofosbuvir with TDF and a PI/r results in increased exposure to TDF. The safety of the increased TDF exposure has not been established. Consider alternative HCV or ARV drugs to avoid increased risk of TDF toxicities. If coadministration is necessary, monitor for TDF-associated adverse reactions.
	ATV (unboosted), ATV/c, DRV/c, DRV/r, LPV/r	↔ PI expected ↔ ledipasvir and sofosbuvir	
	TPV/r	↓ ledipasvir and sofosbuvir expected	**Do not coadminister**.
Sofosbuvir	TPV/r	↓ sofosbuvir expected	**Do not coadminister**.
Sofosbuvir/Velpatasvir	ATV/r	↔ ATV/r ↔ sofosbuvir Velpatasvir AUC ↑ 2.4-fold	No dose adjustment needed.
	DRV/r	↔ DRV/r Sofosbuvir AUC ↓ 28% ↔ velpatasvir	No dose adjustment needed.
	ATV (unboosted), ATV/c, DRV/c, LPV/r	↔ sofosbuvir and velpatasvir expected	No dose adjustment needed.
	TPV/r	↓ sofosbuvir expected ↓ velpatasvir expected	**Do not coadminister**.
Sofosbuvir/Velpatasvir/ Voxilaprevir	ATV (unboosted), ATV/c, ATV/r	**With ATV/r:** • Voxilaprevir AUC ↑ 4.3-fold • Velpatasvir AUC ↑ 93% • Sofosbuvir AUC ↑ 40%	**Do not coadminister**.
	LPV/r	↑ voxilaprevir expected	**Do not coadminister**.
	DRV/c, DRV/r	**With DRV/r:** • Voxilaprevir AUC ↑ 2.4-fold • ↔ DRV/r, velpatasvir, and sofosbuvir	No dose adjustment needed.

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
Sofosbuvir/Velpatasvir/ Voxilaprevir, continued	TPV/r	↓ sofosbuvir expected ↓ velpatasvir expected Effect on voxilaprevir is unknown.	**Do not coadminister**.
Herbal Products			
St. John's Wort	All PIs	↓ PI expected	**Contraindicated.**
Hormonal Therapies			
Contraceptives – Injectable Depot MPA	LPV/r	MPA AUC ↑ 46% and ↔ C_{min}	No dose adjustment needed.
	All other PIs	No data	No dose adjustment needed.
Contraceptives – Oral	ATV (unboosted)	Ethinyl estradiol AUC ↑ 48% Norethindrone AUC ↑ 110%	Prescribe oral contraceptive that contains no more than 30 mcg of ethinyl estradiol[b] or use alternative ARV or contraceptive methods. Oral contraceptives that contain less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.
	ATV/c	Drospirenone AUC ↑ 2.3-fold Ethinyl estradiol AUC ↓ 22%	**Contraindicated with drospirenone-containing hormonal contraceptive due to potential for hyperkalemia.** Use alternative ARV or contraceptive methods.
		↔ ethinyl estradiol AUC and C_{min} ↓ 25% ↔ levonorgestrel	No dose adjustment needed.
	ATV/r	Ethinyl estradiol AUC ↓ 19% and C_{min} ↓ 37% Norgestimate AUC ↑ 85% Norethindrone AUC ↑ 51% and C_{min} ↑ 67%	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol.[c] Oral contraceptives that contain progestins other than norethindrone or norgestimate have not been studied.
	DRV/c	Drospirenone AUC ↑ 1.6-fold Ethinyl estradiol AUC ↓ 30%	Clinical monitoring is recommended due to the potential for hyperkalemia. Use alternative ARV or contraceptive methods.
	DRV/r, LPV/r, TPV/r	Ethinyl estradiol AUC ↓ 37% to 55% Norethindrone AUC ↓ 14% to 34% **With TPV/r:** • ↔ norethindrone AUC	**When Used for Contraception:** • Use alternative ARV or contraceptive methods. **When Used for Other Clinical Indications (e.g., Acne, Menstrual Cycle Regulation):** • Monitor for clinical effectiveness of hormonal therapy.
Contraceptives – Subdermal Implant Etonogestrel	LPV/r	Etonogestrel AUC ↑ 52% and C_{min} ↑ 34%	No dose adjustment needed.
	All other PIs	No data	
Contraceptives – Transdermal Ethinyl Estradiol/ Norelgestromin	LPV/r	↔ LPV Ethinyl estradiol AUC ↓ 45% Norelgestromin AUC ↑ 83%	No dose adjustment needed.
	All other PIs	No data	
Contraceptives – Vaginal Ring Etonogestrel/Ethinyl Estradiol	ATV/r	Ethinyl estradiol AUC ↓ 26% Etonogestrel AUC ↑ 79%	No dose adjustment needed.
	All other PIs	No data	

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 15 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies, continued			
Contraceptives – Vaginal Ring Segesterone/Ethinyl Estradiol	All PIs	No data	Use alternative ARV or contraceptive methods.
Gender-Affirming Therapy	PI/c	↓ or ↑ estradiol possible	Adjust estradiol dose as needed based on clinical effects and endogenous hormone concentrations.
	PI/r	↓ estradiol possible	
	All PIs	↔ goserelin, leuprolide acetate, and spironolactone expected	No dose adjustment needed.
	All PIs	↑ dutasteride possible ↑ finasteride possible	Adjust dutasteride dose as needed based on clinical effects and endogenous hormone concentrations. No dose adjustment needed for finasteride.
	All PIs	↓ testosterone possible	Adjust testosterone dose as needed based on clinical effects and endogenous hormone concentrations.
Menopausal Replacement Therapy	All PIs	↓ or ↑ estrogen possible with estradiol or conjugated estrogen (equine and synthetic)	Adjust estrogen dose as needed based on clinical effects.
	All PIs	↑ drospirenone possible ↑ medroxyprogesterone ↑ micronized progesterone See Hormonal Contraceptives for other progestin-PI interactions	Adjust progestin/progesterone dose as needed based on clinical effects. Because drospirenone is prescribed at a lower dose for menopausal HRT than the products used for hormonal contraceptives, it is not contraindicated with ATV/c products.
Immunosuppressants			
Cyclosporine, Everolimus, Sirolimus, Tacrolimus	All PIs	↑ immunosuppressant expected	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for immunosuppressant-related adverse events. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Lipid-Modifying Agents			
Atorvastatin	ATV (unboosted), ATV/r	↑ atorvastatin possible	Titrate atorvastatin dose carefully and administer the lowest effective dose while monitoring for toxicities.
	ATV/c	Atorvastatin AUC ↑ 9.2-fold and C_{max} ↑ 18.9-fold	**Do not coadminister**.
	DRV/c	Atorvastatin AUC ↑ 3.9-fold and C_{max} ↑ 4.2-fold	Titrate atorvastatin dose carefully and administer the lowest effective dose while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	DRV/r	DRV/r plus atorvastatin 10 mg similar to atorvastatin 40 mg administered alone	Titrate atorvastatin dose carefully and administer the lowest effective dose while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	LPV/r	Atorvastatin AUC ↑ 5.9-fold and C_{max} ↑ 4.7-fold	Titrate atorvastatin dose carefully and administer the lowest effective dose while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	TPV/r	Atorvastatin AUC ↑ 9.4-fold and C_{max} ↑ 8.6-fold	**Do not coadminister**.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 16 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Lipid-Modifying Agents, continued			
Lomitapide	All PIs except TPV/r	↑ lomitapide expected	**Contraindicated.**
	TPV/r	↑ lomitapide expected	Titrate lomitapide dose based on clinical response. Do not exceed lomitapide 30 mg daily.
Lovastatin	All PIs	Significant ↑ lovastatin expected	**Contraindicated.**
Pitavastatin	All PIs	ATV ↑ pitavastatin AUC 31% and C_{max} ↑ 60% ↔ ATV DRV/r ↓ pitavastatin AUC 26% ↔ DRV/r LPV/r ↓ pitavastatin AUC 20% ↔ LPV	No dose adjustment needed.
Pravastatin	ATV/c, ATV/r	No data	Titrate pravastatin dose carefully while monitoring for pravastatin-related adverse events.
	DRV/c, DRV/r	**With DRV/r:** • Pravastatin AUC ↑ 81% following single dose of pravastatin Pravastatin AUC ↑ 23% at steady state	Titrate pravastatin dose carefully while monitoring for pravastatin-related adverse events.
	LPV/r	Pravastatin AUC ↑ 33%	No dose adjustment needed.
Rosuvatatin	ATV/r	Rosuvastatin AUC ↑ 3-fold and C_{max} ↑ 7-fold	Titrate rosuvastatin dose carefully and administer lowest effective dose while monitoring for rosuvastatin-related adverse events. Do not exceed rosuvastatin 10 mg daily.
	ATV/c	Rosuvastatin AUC ↑ 3.4-fold and C_{max} ↑ 10.6-fold	
	DRV/c	Rosuvastatin AUC ↑ 1.9-fold and C_{max} ↑ 3.8-fold	Titrate rosuvastatin dose carefully and administer lowest effective dose while monitoring for rosuvastatin-related adverse events. Do not exceed rosuvastatin 20 mg daily.
	DRV/r	Rosuvastatin AUC ↑ 48% and C_{max} ↑ 2.4-fold	Titrate rosuvastatin dose carefully and administer the lowest effective dose while monitoring for rosuvastatin-related adverse events.
	LPV/r	Rosuvastatin AUC ↑ 2.1-fold and C_{max} ↑ 4.7-fold	Titrate rosuvastatin dose carefully and administer the lowest effective dose. Do not exceed rosuvastatin 10 mg daily.
	TPV/r	Rosuvastatin AUC ↑ 26% and C_{max} ↑ 2.2-fold	No dose adjustment needed.
Simvastatin	All PIs	Significant ↑ simvastatin expected	**Contraindicated.**
Narcotics and Treatment for Opioid Dependence			
Buprenorphine Sublingual, buccal, or implant	ATV (unboosted)	Buprenorphine AUC ↑ 93% Norbuprenorphine (active metabolite) AUC ↑ 76% ↓ ATV possible	**Do not coadminister**.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 17 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Narcotics and Treatment for Opioid Dependence, continued			
Buprenorphine Sublingual, buccal, or implant, continued	ATV/r	Buprenorphine AUC ↑ 66% Norbuprenorphine (active metabolite) AUC ↑ 105%	Monitor for sedation and other signs or symptoms of over-medication. Buprenorphine dose reduction may be necessary. It may be necessary to remove implant and treat with a formulation that permits dose adjustments.
	DRV/r	↔ buprenorphine Norbuprenorphine (active metabolite) AUC ↑ 46% and C_{min} ↑ 71%	No dose adjustment needed. Monitor for buprenorphine-related adverse events. When transferring buprenorphine from transmucosal delivery to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	LPV/r	↔ LPV/r	
	TPV/r	↔ buprenorphine Norbuprenorphine (active metabolite) AUC, C_{max}, and C_{min} ↓ 80% TPV C_{min} ↓ 19% to 40%	Consider monitoring TPV concentration. When transferring buprenorphine from transmucosal delivery to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	PI/c	No data	Titrate buprenorphine dose using the lowest initial dose. Dose adjustment of buprenorphine may be needed. It may be necessary to remove implant and treat with a formulation that permits dose adjustments. Monitor for buprenorphine-related adverse events.
Fentanyl	All PIs	↑ fentanyl possible	Monitor for fentanyl-related adverse events, including potentially fatal respiratory depression.
Lofexidine	ATV (unboosted)	↔ lofexidine expected	No dose adjustment needed.
	PI/c, PI/r	↑ lofexidine possible	Monitor for lofexidine-related adverse events, including symptoms of orthostasis and bradycardia.
Methadone	ATV (unboosted)	↔ ATV	No dose adjustment needed.
	PI/c	No data	Titrate methadone dose using the lowest feasible initial dose. Dose adjustment of methadone may be needed. Monitor for methadone-related adverse events.
	All PI/r	ATV/r and DRV/r ↓ R-methadone[d] AUC 16% to 18% LPV/r ↓ methadone AUC 26% to 53% TPV/r ↓ R-methadone[d] AUC 48%	Opioid withdrawal is unlikely but may occur. Monitor for opioid withdrawal and increase methadone dose as clinically indicated.
Oxycodone	All PIs	LPV/r ↑ oxycodone AUC 2.6-fold Other PIs: ↑ oxycodone expected	Monitor for opioid-related adverse events. Oxycodone dose reduction may be necessary.
Tramadol	All PIs	↑ tramadol expected ↓ M1 (active metabolite) possible	Tramadol dose adjustments may be necessary. Monitor for clinical response and tramadol-related adverse events.
PDE5 Inhibitors			
Avanafil	ATV (unboosted)	No data	Avanafil dose should not exceed 50 mg once every 24 hours.
	PI/c, PI/r	RTV 600 mg twice daily (for 5 days) ↑ avanafil AUC 13-fold and ↑ C_{max} 2.4-fold	**Do not coadminister**.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 18 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors, continued			
Sildenafil	All PIs	DRV/r plus sildenafil 25 mg similar to sildenafil 100 mg alone RTV 500 mg twice daily ↑ sildenafil AUC 1,000%	**For Treatment of Erectile Dysfunction:** • Start with sildenafil 25 mg every 48 hours and monitor for adverse events of sildenafil. **Contraindicated** for treatment of PAH.
Tadalafil	All PIs	RTV 200 mg twice daily ↑ tadalafil AUC 124% TPV/r (first dose) ↑ tadalafil AUC 133%	**For Treatment of Erectile Dysfunction:** • Start with tadalafil 5 mg and do not exceed a single dose of tadalafil 10 mg every 72 hours. Monitor for adverse events of tadalafil. **For Treatment of PAH** *In Patients on a PI >7 Days:* • Start with tadalafil 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. *In Patients on Tadalafil who Require a PI:* • Stop tadalafil ≥24 hours before PI initiation. Seven days after PI initiation, restart tadalafil at 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. *In Patients Switching between COBI and RTV:* • Maintain tadalafil dose. **For Treatment of Benign Prostatic Hyperplasia:** • Maximum recommended daily dose is tadalafil 2.5 mg per day.
Vardenafil	All PIs	RTV 600 mg twice daily ↑ vardenafil AUC 49-fold	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse events of vardenafil.
Sedative/Hypnotics			
Alprazolam, Clonazepam, Diazepam	All PIs	↑ benzodiazepine possible RTV 200 mg twice daily (for 2 days) ↑ alprazolam half-life 222% and ↑ AUC 248%	Consider alternative benzodiazepines, such as lorazepam, oxazepam, or temazepam.
Lorazepam, Oxazepam, Temazepam	All PIs	No data	These benzodiazepines are metabolized via non-CYP450 pathways; thus, there is less interaction potential than with other benzodiazepines.
Midazolam	All PIs	↑ midazolam expected	**Oral midazolam is contraindicated with PIs.** Parenteral midazolam can be used with caution when given as a single dose in a monitored situation for procedural sedation.
Suvorexant	All PIs	↑ suvorexant expected	**Do not coadminister**.
Triazolam	All PIs	↑ triazolam expected RTV 200 mg twice daily ↑ triazolam half-life 1,200% and ↑ AUC 2,000%	**Contraindicated.**
Zolpidem	PI/c, PI/r	↑ zolpidem possible	Initiate zolpidem at a low dose. Dose reduction may be necessary.

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Drugs			
Calcifediol	All PIs	↑ calcifediol possible	Dose adjustment of calcifediol may be required, and serum 25-hydroxyvitamin D, intact PTH, and serum calcium concentrations should be closely monitored.
Cisapride	All PIs	↑ cisapride expected	**Contraindicated.**
Colchicine	All PIs	RTV 100 mg twice daily ↑ colchicine AUC 296% and C_{max} ↑ 184% Significant ↑ colchicine expected with all PIs, with or without COBI or RTV	**For Treatment of Gout Flares:** • Administer a single dose of colchicine 0.6 mg, followed by colchicine 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. **For Prophylaxis of Gout Flares:** • If original dose was colchicine 0.6 mg twice daily, decrease to colchicine 0.3 mg once daily. If dose was 0.6 mg once daily, decrease to 0.3 mg every other day. **For Treatment of Familial Mediterranean Fever:** • Do not exceed colchicine 0.6 mg once daily or colchicine 0.3 mg twice daily. **Do not coadminister in patients with hepatic or renal impairment.**
Dronabinol	All PIs	↑ dronabinol possible	Monitor for dronabinol-related adverse events.
Eluxadoline	All PIs	↑ eluxadoline expected	Administer eluxadoline at a dose of 75 mg twice daily and monitor for eluxadoline-related adverse events.
Ergot Derivatives	All PIs	↑ dihydroergotamine, ergotamine, and methylergonovine expected	**Contraindicated.**
Flibanserin	All PIs	↑ flibanserin expected	**Contraindicated.**

[a] DHA is an active metabolite of artemether.

[b] The following products contain no more than 30 mcg of ethinyl estradiol combined with norethindrone or norgestimate: Lo Minastrin Fe; Lo Loestrin Fe; Loestrin 1/20, 1.5/30; Loestrin Fe 1/20, 1.5/30; Loestrin 24 Fe; Minastrin 24 Fe; Ortho Tri-Cyclen Lo. Generic formulations may also be available.

[c] The following products contain at least 35 mcg of ethinyl estradiol combined with norethindrone or norgestimate: Brevicon; Femcon Fe; Modicon; Norinyl 1/35; Ortho-Cyclen; Ortho-Novum 1/35, 7/7/7; Ortho Tri-Cyclen; Ovcon 35; Tri-Norinyl. Generic formulations may also be available.

[d] R-methadone is the active form of methadone.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key: 17-BMP = beclomethasone 17-monopropionate; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; CCB = calcium channel blocker; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CNS = central nervous system; COBI = cobicistat; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DHA = dihydroartemisinin; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; FPV = fosamprenavir; H2RA = H2 receptor antagonist; HCV = hepatitis C virus; HRT = hormone replacement therapy; IDV = indinavir; INR = international normalized ratio; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MPA = medroxyprogesterone acetate; NFV = nelfinavir; OATP = organic anion-transporting polypeptide; PAH = pulmonary arterial hypertension; PDE5 = Phosphodiesterase Type 5; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; PK = pharmacokinetic; PPI = proton pump inhibitor; PTH = parathyroid hormone; QTc = QT corrected for heart rate; RTV = ritonavir; SQV = saquinavir; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir; VPA = valproic acid